



Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial

Baker, Jason V; Sharma, Shweta; Achhra, Amit C; Bernardino, Jose Ignacio; Bogner, Johannes R; Duprez, Daniel; Emery, Sean; Gazzard, Brian; Gordin, Jonathan; Grandits, Greg; Phillips, Andrew N; Schwarze, Siegfried; Soliman, Elsayed Z; Spector, Stephen A; Tambussi, Giuseppe; Lundgren, Jens; INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group

Published in:

Journal of the American Heart Association

DOI:

[10.1161/JAHA.116.004987](https://doi.org/10.1161/JAHA.116.004987)

Publication date:

2017

Document version

Publisher's PDF, also known as Version of record

Document license:

[CC BY-NC](#)

Citation for published version (APA):

Baker, J. V., Sharma, S., Achhra, A. C., Bernardino, J. I., Bogner, J. R., Duprez, D., Emery, S., Gazzard, B., Gordin, J., Grandits, G., Phillips, A. N., Schwarze, S., Soliman, E. Z., Spector, S. A., Tambussi, G., Lundgren, J., & INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group (2017). Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial. *Journal of the American Heart Association*, 6(5), [e004987]. <https://doi.org/10.1161/JAHA.116.004987>

Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial

Jason V. Baker, MD, MS; Shweta Sharma, MS; Amit C. Achhra, MD, PhD, MPH; Jose Ignacio Bernardino, MD; Johannes R. Bogner, MD; Daniel Duprez, MD, PhD; Sean Emery, PhD; Brian Gazzard, MD; Jonathan Gordin, MD; Greg Grandits, MS; Andrew N. Phillips, PhD; Siegfried Schwarze, Dipl Bio; Elsayed Z. Soliman, MD, PhD; Stephen A. Spector, MD; Giuseppe Tambussi, MD; Jens Lundgren, MD for the INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group*

Introduction—HIV infection and certain antiretroviral therapy (ART) medications increase atherosclerotic cardiovascular disease risk, mediated, in part, through traditional cardiovascular disease risk factors.

Methods and Results—We studied cardiovascular disease risk factor changes in the START (Strategic Timing of Antiretroviral Treatment) trial, a randomized study of immediate versus deferred ART initiation among HIV-positive persons with CD4⁺ cell counts >500 cells/mm³. Mean change from baseline in risk factors and the incidence of comorbid conditions were compared between groups. The characteristics among 4685 HIV-positive START trial participants include a median age of 36 years, a CD4 cell count of 651 cells/mm³, an HIV viral load of 12 759 copies/mL, a current smoking status of 32%, a median systolic/diastolic blood pressure of 120/76 mm Hg, and median levels of total cholesterol of 168 mg/dL, low-density lipoprotein cholesterol of 102 mg/dL, and high-density lipoprotein cholesterol of 41 mg/dL. Mean follow-up was 3.0 years. The immediate and deferred ART groups spent 94% and 28% of follow-up time taking ART, respectively. Compared with patients in the deferral group, patients in the immediate ART group had increased total cholesterol and low-density lipoprotein cholesterol and higher use of lipid-lowering therapy (1.2%; 95% CI, 0.1–2.2). Concurrent increases in high-density lipoprotein cholesterol with immediate ART resulted in a 0.1 lower total cholesterol to high-density lipoprotein cholesterol ratio (95% CI, 0.1–0.2). Immediate ART resulted in 2.3% less BP-lowering therapy use (95% CI, 0.9–3.6), but there were no differences in new-onset hypertension or diabetes mellitus.

Conclusions—Among HIV-positive persons with preserved immunity, immediate ART led to increases in total cholesterol and low-density lipoprotein cholesterol but also concurrent increases in high-density lipoprotein cholesterol and decreased use of blood pressure medications. These opposing effects suggest that, in the short term, the net effect of early ART on traditional cardiovascular disease risk factors may be clinically insignificant."

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00867048. (*J Am Heart Assoc.* 2017;6:e004987. DOI: 10.1161/JAHA.116.004987.)

Key Words: antiretroviral therapy • cholesterol • HIV • risk factor

From the Department of Medicine (J.V.B., D.D.) and Division of Biostatistics, School of Public Health (S. Sharma, G.G.), University of Minnesota, Minneapolis, MN; Division of Infectious Diseases, Hennepin County Medical Center, Minneapolis, MN (J.V.B.); Kirby Institute, University of New South Wales, Sydney, Australia (A.C.A., S.E.); Department of Medicine, Hospital La Paz, IdiPAZ, Madrid, Spain (J.I.B.); Division of Infectious Diseases, MedIV, University Hospital of Munich, Germany (J.R.B.); Chelsea and Westminster Hospital, London, United Kingdom (B.G.); Division of Cardiology, David Geffen School of Medicine at University of California, Los Angeles, CA (J.G.); HIV Epidemiology & Biostatistics Group, University College London, London, United Kingdom (A.N.P.); European AIDS Treatment Group, Berlin, Germany (S. Schwarze); Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, NC (E.Z.S.); Division of Pediatric Infectious Diseases, University of California San Diego and Rady Children's Hospital, San Diego, CA (S.A.S.); San Raffaele Scientific Institute, Milano, Italy (G.T.); CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark (J.L.).

Accompanying Table S1, Figure S1, and Appendix S1 are available at <http://jaha.ahajournals.org/content/6/5/e004987/DC1/embed/inline-supplementary-material-1.pdf>

*A complete list of the INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group members are given in Appendix S1.

Data were presented as a research abstract at the 24th Conference on Retroviruses and Opportunistic Infections, February 22–25, 2016, in Boston, MA.

Correspondence to: Jason V. Baker, MD, MS, 701 Park Avenue, MC G5, Minneapolis, MN 55417. E-mail: baker@umn.edu

Received November 22, 2016; accepted March 30, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

HIV-positive persons are at increased risk for premature cardiovascular disease (CVD),¹ which is currently a leading cause of morbidity and mortality.² Atherosclerotic disease accounts for a substantial proportion of HIV-related CVD among contemporary patients. This atherosclerotic disease manifests as excess risk for coronary heart disease (CHD; eg, myocardial infarction)¹ and stroke,³ and may also contribute to excess risk for heart failure⁴ and sudden cardiac death.⁵

It is well established that features of both HIV infection and certain antiretroviral medications increase the risk for CVD. Some of this excess CVD risk may be caused by long-term systemic inflammation that is mitigated, in part, via antiretroviral therapy (ART)-associated viral suppression,^{6–9} whereas some may be caused by exposure to specific antiretrovirals (eg, certain protease inhibitors [PIs] and abacavir)¹⁰ with potential for adverse changes in blood cholesterol, platelet dysfunction, and/or endothelial dysfunction.^{10–13} Despite unique features of HIV disease, traditional risk factors are highly predictive for CVD among HIV-positive patients^{1,10,14} and can be adversely affected by HIV infection and ART treatment (eg, dyslipidemia).¹⁵

Given the potential for ART to both increase (via drug toxicity and low-density lipoprotein cholesterol [LDL-C] increases) and decrease (via viral suppression and reduced inflammation) atherosclerosis, it is important to study this pathophysiology in the context of randomized comparisons. The START (Strategic Timing of Antiretroviral Treatment) trial is a randomized controlled study of immediate initiation of ART (“immediate” group) versus deferral of ART initiation until CD4⁺ cell counts decline to <350 cells/mm³ or clinical symptoms develop (“deferred” group) among participants naive to ART with CD4⁺ cell counts >500 cells/mm³ at entry.¹⁶ The START trial used an ideal design to compare CVD risk factors between ART-treated and untreated HIV infection in a controlled fashion among persons at low risk for AIDS. CVD events were a component of the composite end point in the START trial, and participants with a recent CVD event (<6 months from entry) were not eligible. The START trial did not have sufficient power to specifically assess CVD event risk (12 and 14 CVD events in the immediate and deferred groups, respectively).¹⁶ In this study, we characterized the influence of immediate versus deferred ART on CVD risk factor changes and incidence of CVD-related comorbidities.

Methods

Study Design and Data Collection

The design and primary findings from the START trial have been described.^{16,17} The START protocol was approved by the human subjects institutional review committee at the University of Minnesota and at all international coordinating centers and participating clinical sites. After informed consent was

obtained, data collection occurred at baseline, months 1 and 4, and every 4 months thereafter. Participants were instructed to fast (minimum of 8 hours) for annual blood draws. Laboratory measures were performed using standardized clinical assays at the sites. HIV RNA level, CD4⁺ cell count, weight, and blood pressure (BP) were ascertained at every study visit. The BP values used in the analyses were the average of 2 measurements separated by a brief rest. Glucose and serum lipid levels (total cholesterol, high-density lipoprotein cholesterol [HDL-C], LDL-C, and triglycerides) and concomitant medication use were obtained at baseline and annually. At screening, clinicians together with participants prespecified the intended ART regimen a participant would initiate if randomized to the immediate group. This regimen was required to include 2 background nucleoside reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted PI, or an integrase strand transfer inhibitor (INSTI). Defining subgroups by the prespecified ART regimen allowed a randomized comparison between the immediate and deferred groups among those who were designated to start the same antiretroviral medication. Data for this report included visits up to the START trial unblinding date of May 26, 2015.

Clinical Comorbidities and Risk Factor Scores

Dyslipidemia was defined as an LDL-C level ≥ 160 mg/dL or use of lipid-lowering therapy. Hypertension was defined as a systolic BP ≥ 140 mm Hg, a diastolic BP ≥ 90 mm Hg, or use of BP-lowering therapy. Diabetes mellitus was defined as a fasting glucose level >126 mg/dL, use of medication for diabetes mellitus, or a clinical diagnosis of diabetes mellitus (adjudicated as confirmed or probable). Body mass index (BMI) was computed using visit-specific weight and baseline height. Ten-year risk scores were calculated at baseline and updated during follow-up for the following^{18–21}: (1) Framingham Risk Score for a CVD or CHD event; (2) D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) risk score for a CVD or CHD event; and (3) the pooled cohort risk assessment for an atherosclerotic CVD event.

Statistical Methods

The mean changes from baseline between the immediate and deferred groups for continuous measures were compared using longitudinal mixed models with random intercepts, including treatment group, visit, and baseline value in the model. The differences between groups for the prevalence of binary measures were compared using generalized estimating equations (binomial regression) with treatment group, visit, and baseline prevalence in the model. Histograms showed

that total cholesterol, LDL-C, HDL-C, and BP were approximately normally distributed and were analyzed untransformed. The proportional hazards assumption was tested using log-time as a covariate in the model. Comparisons within subgroups defined by prespecified ART drug or class (efavirenz [EFV], PI, or INSTI) are reported. EFV-based ART was included as a subgroup in analyses by ART class, given that EFV represented 95% of the NNRTI use in the START trial. Incidence for binary risk factors was determined in participants without that condition at baseline using a single factor for treatment in Cox regression models. To directly compare treated versus untreated HIV infection we repeated the analyses by excluding immediate group participants who never started ART ($n=39$) and censoring the deferred group at the time of ART initiation. Analyses were performed using SAS software version 9.3 (SAS Institute Inc) and R software version 3.2.3 (R Foundation for Statistical Computing).

Results

Participant Characteristics

A total of 4685 HIV-positive individuals from 215 sites in 35 countries were enrolled into the START trial. The median age of participants was 36 years and 27% were female (Table 1).²² Self-reported race/ethnicity reflected global enrollment from the United States (11%), South America and Mexico (25%), Europe, Israel and Australia (35%), Africa (21%), and Asia (8%). The CD4⁺ cell count at entry was 651 cells/mm³, and the median time since HIV diagnosis was 1 year. Mean (SD) and median [interquartile range] follow-up time was 3.0 (1.2) and 2.8 [2.1–3.9] years, respectively, with no difference in follow-up time between the immediate and deferred groups. Baseline characteristics did not differ between groups (Table 1). In addition to a high smoking prevalence, START trial participants were at low risk for CVD based on the median values for BMI, BP, cholesterol, and CVD/CHD risk scores.

The percentage of participants taking ART during follow-up is presented in Figure 1; 98% of the immediate group and 48% of the deferred group initiated ART, with a median time to initiation of 36 months in the deferred group. The percentage of follow-up time spent taking ART was 94% and 28% for the immediate and deferred groups, respectively. The frequency of specific antiretrovirals in the initial ART regimen reflects contemporary clinical practice (Table S1). Among the 2287 immediate group participants who initiated therapy, ART included tenofovir disoproxil fumarate in 89%, an NNRTI in 77% (73% EFV), a ritonavir-boosted PI in 19% (10% atazanavir and 7% darunavir), and an INSTI in 5% (4% raltegravir); corresponding values for the 1134 deferred group participants who initiated therapy

included tenofovir disoproxil fumarate in 89%, an NNRTI in 64% (51% EFV), a PI in 22% (11% darunavir), and an INSTI in 14% (8% raltegravir).

Changes in Serum Cholesterol Levels and Lipid-Lowering Therapy

Mean changes in lipid levels (Figure 2) and the incidence of dyslipidemia (Figure 3) are presented for each group. Compared with the ART deferral group, the immediate ART group had 11 mg/dL higher total cholesterol (95% CI, 10–13), 6 mg/dL higher LDL-C (95% CI, 4–7), and 5 mg/dL higher HDL-C (95% CI, 4–5) levels. The rise in total cholesterol and LDL-C in the immediate group was associated with a 1.2% greater use of lipid-lowering therapy (95% CI, 0.2–2.2) and a higher incidence rate of dyslipidemia (hazard ratio, 1.7; 95% CI, 1.4–2.02). Among the 346 participants taking lipid-lowering therapy at entry or during follow-up, 68% were taking a statin. Increases in HDL-C levels resulted in a marginally lower total cholesterol to HDL-C ratio in the immediate versus the deferred group (−0.1; 95% CI, −0.2 to −0.1). When HDL <40 mg/dL was included in the criteria for dyslipidemia, 49% (2283) of participants had dyslipidemia at study entry. When including low HDL in the definition, the incidence rate for dyslipidemia was lower in the immediate ART group compared with the deferred ART group (hazard ratio, 0.7; 95% CI, 0.6–0.8) (Figure 3). Immediate ART also resulted in higher triglyceride (8 mg/dL; 95% CI, 3–12) and non-HDL-C (7 mg/dL; 95% CI, 5–8) levels than deferred ART. Participants were fasting for ≈91% of blood draw visits and the findings were similar when analyses were restricted to fasting specimens. In analyses of treated versus untreated HIV infection, the treatment differences in lipid changes from baseline were of higher magnitude but similar.

Table 2 presents analyses of subgroups defined by prespecified ART, with comparisons for EFV-, PI-, and INSTI-based ART. These data represent the effect of starting a specific antiretroviral when compared with a group randomized to defer ART but who intended to start the same antiretroviral medication or class. Time spent during follow-up taking the prespecified ART varied between 75% and 80% for the immediate group and 15% and 20% for the deferred group. There was a significant interaction between the prespecified ART regimen and the treatment difference for several cholesterol measures. Specifically, participants who prespecified EFV use had a greater difference in both total cholesterol and HDL-C level between the immediate and deferred groups, when compared with those who prespecified PI use. Similarly, when compared with those who prespecified an INSTI, the EFV subgroup had greater differences in total cholesterol, LDL-C, and HDL-C levels between the immediate and deferred

Table 1. Baseline Characteristics of Patients in the START Trial (n=4685)

	Median [IQR] or % (No.)
Demographics	
Age, y	36 [29–44]
Female sex	26.8 (1257)
Race	
Asian	8.3 (388)
Black	30.1 (1410)
Latino/Hispanic	13.6 (638)
White	44.5 (2086)
Other	3.5 (163)
HIV history and laboratory	
Time known to be HIV positive, y	1.0 [0.4–3.1]
CD4, cells/mm ³ *	651 [584–765]
Nadir CD4, cells/mm ³ †	553 [488–654]
HIV RNA, copies/mL	12 759 [3019–43 391]
Clinical measures	
BMI, kg/m ²	24.6 [22.1–27.9]
Systolic BP, mm Hg	120 [111–130]
Diastolic BP, mm Hg	76 [70–83]
Risk factors	
Current smoker	31.9 (1496)
Diabetes mellitus	3.3 (156)
Prior CVD diagnosis‡	0.8 (36)
Hypertension	19.2 (898)
BP-lowering drugs	8.1 (281)
Dyslipidemia	8.2 (386)
Lipid-lowering drugs	3.5 (163)
Glucose and lipids	
Glucose, mg/dL	85 [79–92]
Total cholesterol, mg/dL	168 [144–195]
LDL-C, mg/dL	102 [82–124]
HDL-C, mg/dL	41 [35–50]
Triglycerides, mg/dL	97 [71–142]
Total cholesterol to HDL-C ratio	4.0 [3.2–5.0]
Non-HDL-C, mg/dL	124 [102–150]
10-year predicted risk scores	
CVD FRS, %§	2.3 [0.7–6.5]
CHD FRS, %§	1.9 [0.5–5.0]
CVD D:A:D, %	1.8 [0.9–3.5]
CHD D:A:D, %	1.4 [0.7–2.9]
Pooled cohort ASCVD, %¶	2.2 [1.0–4.4]
Lifetime ASCVD risk score, %¶	31.2 [15.6–39.6]

Continued

Table 1. Continued

	Median [IQR] or % (No.)
Prespecified ART regimen	
EFV	75.1 (3516)
PI	17.4 (815)
INSTI	3.9 (183)
Non-EFV NNRTI	3.7 (171)

ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; EFV, efavirenz; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; START, Strategic Timing of Antiretroviral Treatment.

*Average of 2 screening values.

†Documented in participant record.

‡Diagnosis of any of the following prior to randomization: myocardial infarction, stroke, coronary heart disease requiring drug treatment, coronary revascularization, congestive heart failure, or peripheral arterial disease.

§Framingham Risk Score (FRS) equations in Anderson et al.¹⁸

||Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) score equations in Friis-Møller et al.¹⁹

¶Atherosclerotic cardiovascular disease (ASCVD) risk equation in Goff et al.²⁰

*Lifetime ASCVD risk score in Berry et al.²²

groups. Notably, there was no difference in any lipid parameters between immediate and deferred ART among the subgroup that prespecified INSTI use. In analyses of treated versus untreated HIV infection, the magnitude of the treatment differences in lipid changes from baseline was higher for EFV- and PI-based ART.

Changes in BP

When compared with patients who underwent ART deferral, those who took immediate ART demonstrated no difference in systolic BP, a lower diastolic BP that was not significant (Figure 2), and a lower prevalence of BP-lowering therapy (−2.2%; 95% CI, −3.6 to −0.93). At entry, 19% of participants had hypertension (per our definition), and when new-onset hypertension rates were compared between the immediate and deferred groups, the hazard ratio for reduced incidence of hypertension did not reach significance (0.87; 95% CI, 0.74–1.02; [*P*=0.10]) (Figure 3). After analyses of treated versus untreated HIV infection, there remained no difference in use of BP-lowering therapy or incident hypertension between the groups, whereas diastolic BP was significantly lower in the immediate ART group (−0.4; 95% CI, −0.1 to −0.7 [*P*=0.02]).

Changes in Metabolic Parameters

Patients in the immediate group had a higher mean glucose level of 2 mg/dL (95% CI, 1–3) than patients in the deferred group (Figure S1), but there was no difference in the incidence

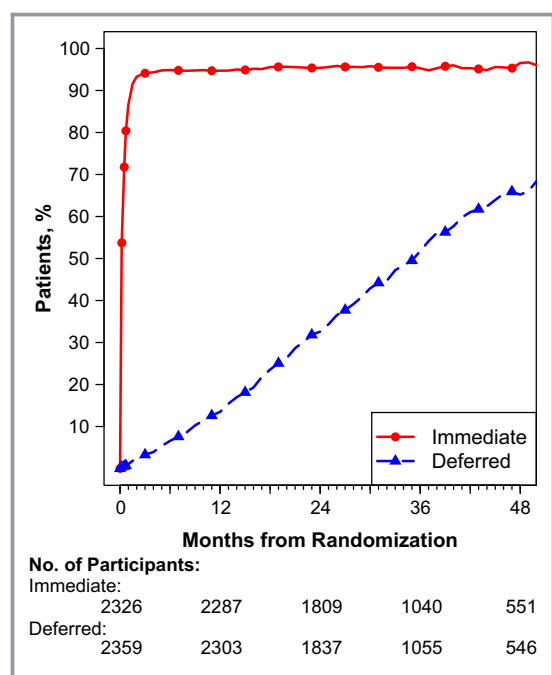


Figure 1. Antiretroviral therapy (ART) use by treatment group in the START (Strategic Timing of Antiretroviral Treatment) trial (n=4685). Shown is the percentage of participants taking ART by follow-up month in the immediate and deferred ART groups. Data were previously reported but the results shown here are truncated at month 48.¹⁶

of type 2 diabetes mellitus (Figure 3). In contrast, BMI was significantly lower among patients in the immediate versus deferred groups (-0.2 kg/m^2 ; 95% CI, -0.3 to -0.1), although the magnitude of this effect is of unclear clinical significance (Figure S1). The treatment effect on BMI appeared greatest early after randomization ($P < 0.001$ for interaction of treatment group by follow-up time). When comparing subgroups defined by prespecified ART regimen, BMI showed a significantly greater decline (with immediate versus deferred ART) among patients in the EFV (-0.3 kg/m^2 ; 95% CI, -0.4 to -0.2) versus PI (-0.1 kg/m^2 ; 95% CI, -0.2 to 0.1) subgroups. Finally, there was no evidence of an interaction between prespecified ART regimen and a treatment effect for serum glucose or incident diabetes mellitus.

Differences in Risk Factor Profile and Predicted Risk Scores

We studied the effect of immediate ART on CVD and CHD predicted risk scores. Smoking contributed the most to predicted risk, but rates did not differ between treatment groups during follow-up (Figure S1). The mean difference between groups was not significant for the atherosclerotic CVD pooled cohort 10-year risk score (-0.1 ; 95% CI, -0.2 to -0.1), the Framingham Risk Score 10-year CVD (-0.1 ; 95%

CI, -0.3 to -0.0), or the Framingham Risk Score 10-year CHD (-0.1 ; 95% CI -0.3 to -0.0), but was slightly higher in the immediate group for the D:A:D 10-year CVD (0.2 ; 95% CI, 0.1 – 0.3) and CHD (0.1 ; 95% CI, 0.1 – 0.2) estimates. Differences in the D:A:D scores were caused primarily by the fact that this score considers exposure to certain antiretrovirals (eg, abacavir, lopinavir); there were no differences when censoring participants after initiation of these antiretrovirals. After analyses of patients with treated versus untreated HIV infection, the treatment differences in the Framingham Risk Score estimates were of a similar low magnitude but reached statistical significance.

Discussion

The START trial is the first randomized clinical investigation to study the impact of immediate ART initiation, when compared with deferral, on CVD risk factors among a large global HIV-positive cohort with high CD4^+ cell counts. It is in this context that understanding and mitigating risk for CVD becomes a high priority in clinical practice. When compared with ART deferral, ART initiation increased total cholesterol and LDL-C levels and use of lipid-lowering therapy, but also increased HDL-C level and resulted in a decline in total cholesterol to HDL-C ratio. Changes in CVD or CHD prediction scores with immediate versus deferred ART were minimal or nonsignificant.

A well-described consequence of untreated HIV infection is a decline in most serum lipids levels (the primary exception being an elevation in triglycerides), with ART initiation then leading to a compensatory increase in total cholesterol and LDL-C levels to a degree that often varies by regimen.^{15,23,24} We present novel randomized data quantifying the absolute effect of ART initiation on serum lipids, when compared with initially untreated HIV disease. Increases in total cholesterol were greatest among the subgroups that prespecified EFV. Prior studies have lacked a comparison group of untreated persons, but have reported greater within-participant increases in total cholesterol (mean 19 and 55 mg/dL) and LDL-C (mean 4 and 23 mg/dL) levels 1 year after starting NNRTI- (eg, EFV) or PI-based ART, when compared with the changes reported in the START trial.^{15,25,26} It is unclear whether the greater increases in LDL-C level with EFV-based ART reflects greater CVD risk, given that increases in HDL-C level were also greater with EFV and that epidemiologic data demonstrate that exposure to certain PIs, but not to NNRTIs (eg, EFV), are associated with greater risk for myocardial infarction.^{10,27}

Data from comparative antiretroviral trials have shown the greatest rises in HDL-C level after starting EFV (73% in the START trial) or tenofovir (89% in the START trial), with the effect from INSTIs (5% in the START trial) being

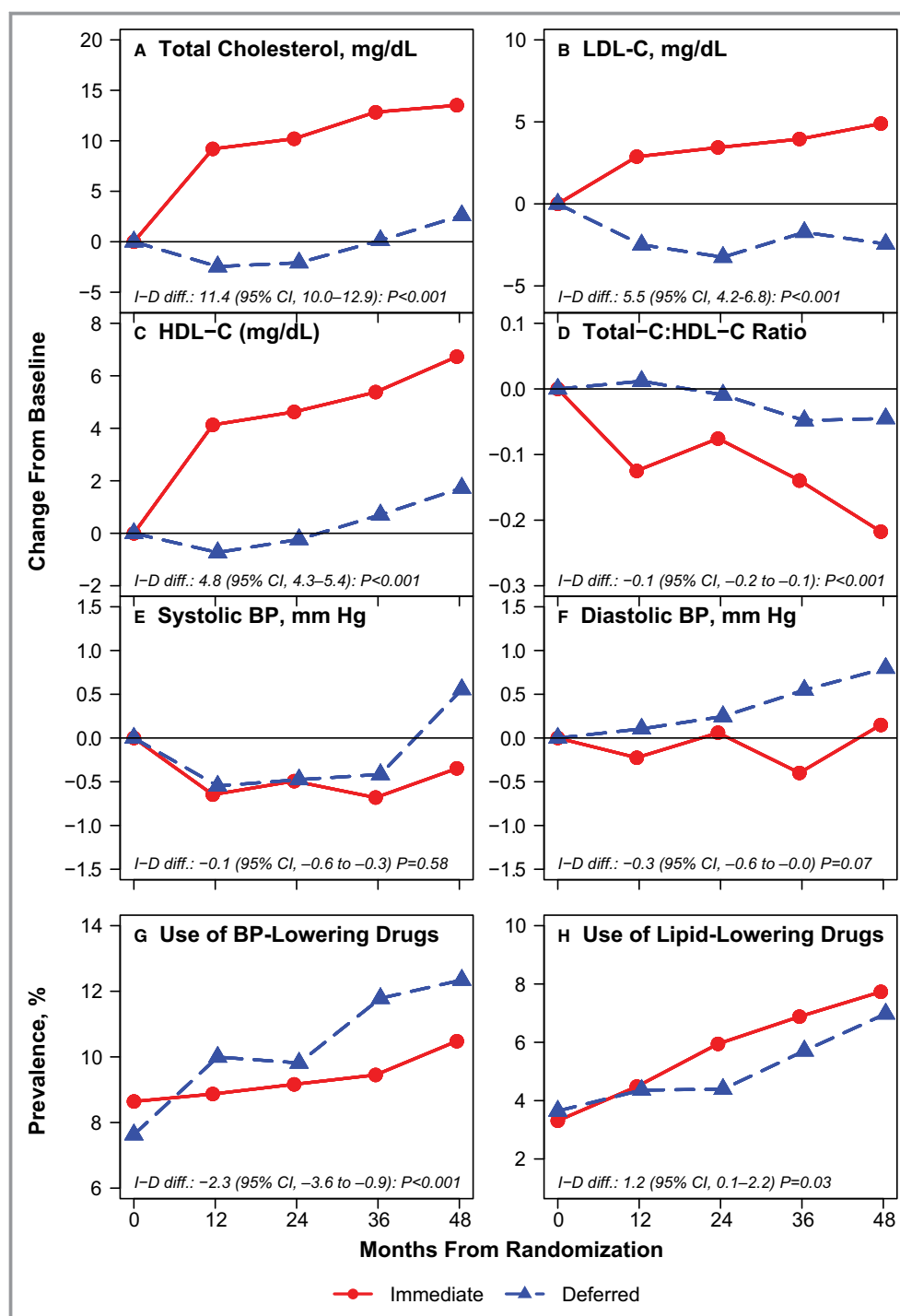


Figure 2. Cardiovascular risk factor changes by treatment group. Shown in the first 3 rows are the unadjusted mean changes from baseline at annual visits for participants in the immediate (I) and deferred (D) antiretroviral therapy (ART) groups for the following measures: total cholesterol (A), low-density lipoprotein cholesterol (LDL-C; B), high-density lipoprotein cholesterol (HDL-C; C), total cholesterol to HDL-C ratio (D), systolic blood pressure (BP; E), and diastolic BP (F). Presented within (A through F) are the estimated mean differences (with 95% CIs and P values) during follow-up between the 2 groups (I minus D), adjusting for the baseline value and visit from longitudinal mixed models. Shown in the last row is the unadjusted prevalence (percentage) at baseline and follow-up annual visits for participants in both ART groups for use of BP-lowering drugs (G) and lipid-lowering drugs (H). Presented within (G and H) are the overall estimated differences in prevalence during follow-up (with 95% CIs and P values) between the 2 groups (I minus D), adjusting for the baseline prevalence and visit from generalized estimating equations. Figures are truncated at month 48.

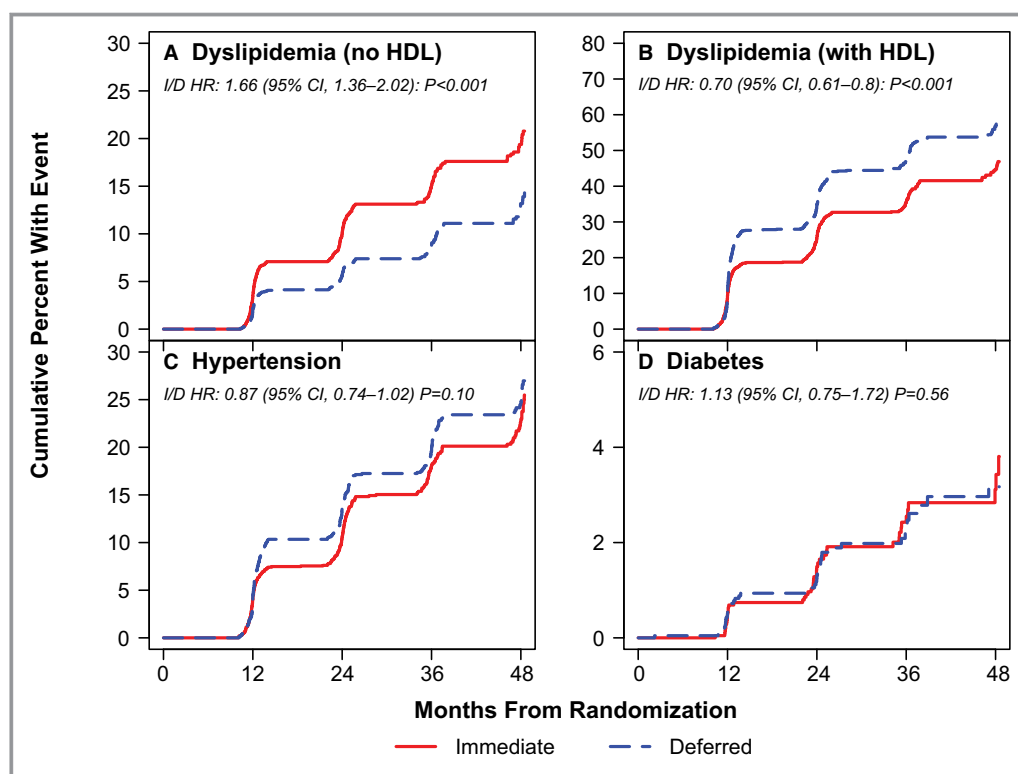


Figure 3. Cumulative incidence of comorbid conditions by treatment group. Shown are Kaplan–Meier estimates of the cumulative incidence of participants with dyslipidemia, excluding high-density lipoprotein (HDL) in the definition (A), dyslipidemia, including HDL <40 mg/dL in the definition* (B), hypertension† (C), and diabetes mellitus (D) during follow-up for participants in the immediate (I) and deferred (D) antiretroviral therapy (ART) groups. Presented within the figures are the estimated hazard ratios (HRs) for the immediate (I) vs deferred (D) groups (with 95% CIs and *P* values) from Cox proportional hazards regression models. Figures are truncated at month 48. The cumulative incidence plots have jumps annually because measurements were obtained only at annual visits. *A total of 2203 (49%) START (Strategic Timing of Antiretroviral Treatment) trial participants had dyslipidemia at baseline when including the criteria of HDL <40 mg/dL. The incidence computation during follow-up for this definition is limited to the 2402 participants without baseline dyslipidemia. †For the incidence computation, an individual was defined as being hypertensive at the first visit when systolic blood pressure (BP) was ≥ 140 mm Hg, diastolic BP was ≥ 90 mm Hg, or BP medication use was reported. In some individuals classified as hypertensive based on BP alone, the BP may be lower at subsequent visits. This definition leads to a higher incidence.

mixed.^{25,26,28–32} Our findings support that ART initiation with EFV-based ART led to the greatest increases in HDL-C level. Furthermore, the degree of HDL-C level increase attributable to initiating EFV-based ART was large enough to result in a concurrent decline in the ratio of total cholesterol to HDL-C, which was not observed for PI- or INSTI-based ART. The differential effect on HDL-C level by ART regimen and lack of significant INSTI effects on any blood lipids suggests that cholesterol changes may, in part, be mediated via effects other than those related to HIV viral suppression.

Multiple factors contribute to dyslipidemia among ART-treated HIV-positive patients, including altered hepatic synthesis, inflammation, oxidative stress, direct drug toxicity (eg, PI binding of the LDL-C receptor protein), and possibly genetic factors.^{23,33–35} The modest degree of ART-associated

increases in total cholesterol and LDL-C levels described in the START trial was surprising, although, as noted, may be caused by the fact that previous estimates cannot isolate the net effect of ART versus no ART. One important caveat to the increase in dyslipidemia with immediate ART in the START trial was that if low HDL level was included as criteria, then dyslipidemia was less with immediate ART. Another important difference between findings from the START trial and most prior ART trials is the health of the study population, raising the question of whether ART-related effects on serum lipids may be decreased when initiating treatment earlier in HIV disease. Still, the effect of ART treatment on blood lipid levels in the START trial emphasizes that cholesterol should remain a key target for CVD risk factor modification within this population.

Table 2. Overall Treatment Difference (I–D) in Metabolic Parameters by Subgroups Defined by Prespecified ART Regimen at Baseline

Measure	Prespecified ART			Interaction P Value [†]
	EFV (n=3516)	PI (n=815)	INSTI (n=183)	
	I–D Mean Difference* (95% CI)	I–D Mean Difference* (95% CI)	I–D Mean Difference* (95% CI)	
Total cholesterol, mg/dL	13.2 (11.5–14.9)	8.7 (5.2–12.1)	–2.4 (–10.1 to 5.3)	<0.001
LDL-C, mg/dL	6.5 (5.0–7.9)	3.7 (0.7–6.7)	–1.1 (–7.8 to 5.7)	0.036
HDL-C, mg/dL	5.8 (5.2–6.4)	2.2 (0.9–3.5)	0.4 (–2.5 to 3.4)	<0.001
Total cholesterol to HDL-C ratio	–0.2 (–0.2 to –0.1)	–0.0 (–0.2 to 0.1)	–0.2 (–0.5 to 0.2)	0.13

EFV indicates efavirenz; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; LDL-C, low-density lipoprotein cholesterol; PI, protease inhibitor.

*Mean differences (immediate [I] minus deferred [D]) during all follow-up using longitudinal mixed models adjusting for baseline level and visit.

[†]2 df P value for interaction between treatment group and 3 prespecified antiretroviral therapy (ART) regimens comparing the I–D treatment difference among subgroups.

Although immediate ART initiation did not lead to significant changes in BP or incident hypertension, the use of BP-lowering therapy and the prevalence of hypertension were less with immediate ART. Reasons for this discrepancy are unclear, but incident hypertension does not reflect influences on the use of BP-lowering therapy among patients with known hypertension at entry. Associations between inflammatory cytokines and vascular stiffness provide some biologic pretense for why suppressing HIV replication may reduce the need for BP therapy.^{36–39} However, if a true ART-treatment effect on absolute BP was present but not detected in this study (eg, type 2 error), it is unlikely to be clinically significant.

ART is well known to be associated with body composition changes, although contemporary ART regimens are less toxic than early-era antiretrovirals.^{40–42} In the START trial, immediate ART initiation led to a clinically insignificant increase in serum glucose (ie, with no change in incidence of diabetes mellitus), but was also associated with a marginally lower BMI. The BMI findings are counter to prior observations of ART increases in abdominal fat, but, importantly, BMI assessments do not delineate between changes in visceral and subcutaneous fat.^{41,43} In addition, the relative immune preservation in the START trial may be important in that toxicity from a given antiretroviral medication may be more pronounced among patients with more severe immune depletion. This hypothesis was suggested by notable findings from HOPS (the HIV Outpatient Study), in which starting ART at higher (versus lower) CD4⁺ cell counts reduced the incidence of peripheral neuropathy, even when using antiretrovirals well known to cause neuropathy.⁴⁴

Ultimately, the net effect of early ART initiation on traditional risk factors appeared to have a clinically insignificant effect on CVD and CHD risk algorithms. While 10-year CVD/CHD predicted risk remained low in absolute terms, the estimated lifetime atherosclerotic CVD risk at study entry among this younger population was still >30%,²² reinforcing

that traditional risk factor management remains an important strategy to mitigate the cumulative effects of HIV, ART, and advancing age over time. However, it does remain unclear how well the atherosclerotic CVD lifetime risk estimation reflects true clinical risk in this context as it has not been validated among HIV-positive persons.

Study Limitations

These analyses have several limitations. We did not directly assess or characterize other potentially important CVD risk mechanisms (eg, HIV-related systemic inflammation) or potential mechanisms of ART toxicity. There was potential for confounding in terms of baseline lipid levels influencing the choice of ART regimen; however, we did not see evidence for this, as the prevalence of prespecified PI (17%) was the same for persons with and without hyperlipidemia at baseline. Also, analyses focused on the INSTI subgroup were limited by small numbers. Finally, we are not able to characterize whether the ART-related changes in CVD risk factors will translate to differences in clinical event risk caused by the limited number of events in the START trial, although findings to date have not detected a significant effect of immediate versus deferred ART on risk for CVD events (HR, 0.84; 95% CI, 0.39–1.81).¹⁶

Conclusions

These data, among a diverse global population of HIV-positive persons with high CD4 cell counts, suggest that immediate ART initiation has both positive and negative influences on CVD risk factors. Ultimately, long-term follow-up in the START trial is needed to determine the net effect of ART treatment initiation for CVD event risk among HIV-positive individuals with preserved immunity.

Acknowledgments

The authors would like to specifically thank the participants in the START trial. See supplemental material for the complete listing of the INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group (also published in *N Engl J Med*. 2015;373:795–807).

Sources of Funding

The START trial (NCT00867048) is registered at clinicaltrials.gov. The START trial is primarily funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under award numbers UM1-AI068641 and UM1-AI120197, with additional support from the NIH Clinical Center; National Cancer Institute; National Heart, Lung, and Blood Institute; Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Institute of Mental Health; National Institute of Neurological Disorders and Stroke; National Institute of Arthritis and Musculoskeletal and Skin Diseases; Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (France); National Health and Medical Research Council (Australia); National Research Foundation (Denmark); Bundesministerium für Bildung und Forschung (Germany); European AIDS Treatment Network; Medical Research Council (United Kingdom); National Institute for Health Research; National Health Service (United Kingdom); and University of Minnesota. Antiretroviral drugs are donated to the central drug repository by AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Janssen Scientific Affairs, and Merck. Dr Gordin is supported by the NIH Cardiovascular Scientist Training Program under award number T32 HL007895.

Disclosures

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr Phillips received fees for speaking at 2 meetings sponsored by Gilead Sciences, for consulting from GSK Biologicals, and for attendance at an advisory board membership from AbbVie. The remaining authors declare no relevant financial interests.

References

- Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doeblen D, Bryant K, Justice AC. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622.
- Miller CJ, Baker JV, Bormann AM, Erlandson KM, Huppler Hullsiek K, Justice AC, Neuhaus J, Paredes R, Petoumenos K, Wentworth D, Winston A, Wolfson J, Neaton JD; INSIGHT SMART Study Group; ESPRIT Study Group. Adjudicated morbidity and mortality outcomes by age among individuals with HIV infection on suppressive antiretroviral therapy. *PLoS One*. 2014;9:e95061.
- Sico JJ, Chang CC, So-Armah K, Justice AC, Hylek E, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, Rimland D, Bidwell Goetz M, Butt AA, Rodriguez-Barradas MC, Gibert C, Leaf D, Brown ST, Samet J, Kazis L, Bryant K, Freiberg MS; Veterans Aging Cohort Study. HIV status and the risk of ischemic stroke among men. *Neurology*. 2015;84:1933–1940.
- Butt AA, Chang CC, Kuller L, Goetz MB, Leaf D, Rimland D, Gibert CL, Oursler KK, Rodriguez-Barradas MC, Lim J, Kazis LE, Gottlieb S, Justice AC, Freiberg MS. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med*. 2011;171:737–743.
- Tseng ZH, Secemsky EA, Dowdy D, Vittinghoff E, Moyers B, Wong JK, Havlir DV, Hsue PY. Sudden cardiac death in patients with human immunodeficiency virus infection. *J Am Coll Cardiol*. 2012;59:1891–1896.
- Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Nixon D, Paton NI, Prineas RJ, Neaton JD; INSIGHT SMART Study Group. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. *PLoS One*. 2012;7:e44454.
- Triant VA, Regan S, Lee H, Sax PE, Meigs JB, Grinspoon SK. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. *J Acquir Immune Defic Syndr*. 2010;55:615–619.
- Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fatkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, Rappoport C. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355:2283–2296.
- Baker JV, Neuhaus J, Duprez D, Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Nixon D, Paton NI, Neaton JD. Changes in inflammatory and coagulation biomarkers: a randomized comparison of immediate versus deferred antiretroviral therapy in patients with HIV infection. *J Acquir Immune Defic Syndr*. 2011;56:36–43.
- Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiebaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735.
- Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, Sosman JM. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation*. 2001;104:257–262.
- Shankar SS, Dube MP, Gorski JC, Klaunig JE, Steinberg HO. Indinavir impairs endothelial function in healthy HIV-negative men. *Am Heart J*. 2005;150:933.
- Satchell CS, O'Halloran JA, Cotter AG, Peace AJ, O'Connor EF, Tedesco AF, Feeney ER, Lambert JS, Sheehan GJ, Kenny D, Mallon PW. Increased platelet reactivity in HIV-1-infected patients receiving abacavir-containing antiretroviral therapy. *J Infect Dis*. 2011;204:1202–1210.
- Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92:2506–2512.
- Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289:2978–2982.
- INSIGHT Start Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fätkenheuer G, Llibre JM, Molina JM, Munderi P, Schechter M, Wood R, Klingman KL, Collins S, Lane HC, Phillips AN, Neaton JD. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373:795–807.
- Babiker AG, Emery S, Fatkenheuer G, Gordin FM, Grund B, Lundgren JD, Neaton JD, Pett SL, Phillips A, Touloumi G, Vjecha MJ; INSIGHT START Study Group. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. *Clin Trials*. 2013;10:S5–S36.
- Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293–298.
- Friis-Møller N, Thiebaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil*. 2010;17:491–501.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Selke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/

- American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73.
21. Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglius ML, Garside D, Dyer AR, Liu K, Greenland P. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA*. 1999;282:2012–2018.
 22. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329.
 23. Kelesidis T, Currier JS. Dyslipidemia and cardiovascular risk in human immunodeficiency virus infection. *Endocrinol Metab Clin North Am*. 2014;43:665–684.
 24. Grunfeld C, Pang M, Doerrier W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab*. 1992;74:1045–1052.
 25. Hill A, Sawyer W, Gazzard B. Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels. *HIV Clin Trials*. 2009;10:1–12.
 26. Quercia R, Roberts J, Martin-Carpenter L, Zala C. Comparative changes of lipid levels in treatment-naïve, HIV-1-infected adults treated with dolutegravir vs. efavirenz, raltegravir, and ritonavir-boosted darunavir-based regimens over 48 weeks. *Clin Drug Invest*. 2015;35:211–219.
 27. Rosenblatt L, Farr AM, Johnston SS, Nkhoma ET. Risk of cardiovascular events among patients initiating efavirenz-containing versus efavirenz-free antiretroviral regimens. *Open Forum Infect Dis*. 2016;3:ofw061.
 28. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, Godfrey C, Jahed NC, Myers L, Katzenstein D, Farajallah A, Rooney JF, Pappa KA, Woodward WC, Patterson K, Bolivar H, Benson CA, Collier AC; AIDS Clinical Trials Group Study A5202 Team. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011;154:445–456.
 29. DeJesus E, Rockstroh JK, Henry K, Molina JM, Gathe J, Ramanathan S, Wei X, Yale K, Szwarcberg J, White K, Cheng AK, Kearney BP; Team GSS. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. 2012;379:2429–2438.
 30. Ofotokun I, Na LH, Landovitz RJ, Ribaldo HJ, McComsey GA, Godfrey C, Aweeka F, Cohn SE, Sagar M, Kuritzkes DR, Brown TT, Patterson KB, Para MF, Leavitt RY, Villasis-Keever A, Baugh BP, Lennox JL, Currier JS; AIDS Clinical Trials Group (ACTG) A5257 Team. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis*. 2015;60:1842–1851.
 31. Wohl DA, Cohen C, Gallant JE, Mills A, Sax PE, DeJesus E, Zolopa A, Liu HC, Plummer A, White KL, Cheng AK, Rhee MS, Szwarcberg J; GS-US-236-0102 Study Team. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65:e118–e120.
 32. Rockstroh JK, DeJesus E, Lennox JL, Yazdanpanah Y, Saag MS, Wan H, Rodgers AJ, Walker ML, Miller M, DiNubile MJ, Nguyen BY, Teppler H, Leavitt R, Sklar P; STARTMRK Investigators. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63:77–85.
 33. Mujawar Z, Rose H, Morrow MP, Pushkarsky T, Dubrovsky L, Mukhamedova N, Fu Y, Dart A, Orenstein JM, Bobryshev YV, Bukrinsky M, Sviridov D. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol*. 2006;4:e365.
 34. Feingold KR, Grunfeld C. The acute phase response inhibits reverse cholesterol transport. *J Lipid Res*. 2010;51:682–684.
 35. Stein JH, Komarow L, Cotter BR, Currier JS, Dube MP, Fichtenbaum CJ, Gerschenson M, Mitchell CK, Murphy RL, Squires K, Parker RA, Torriani FJ. Lipoprotein changes in HIV-infected antiretroviral-naïve individuals after starting antiretroviral therapy: ACTG Study A5152s stein: lipoprotein changes on antiretroviral therapy. *J Clin Lipidol*. 2008;2:464–471.
 36. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension*. 2005;46:1118–1122.
 37. Schnabel R, Larson MG, Dupuis J, Lunetta KL, Lipinska I, Meigs JB, Yin X, Rong J, Vita JA, Newton-Cheh C, Levy D, Keaney JF Jr, Vasan RS, Mitchell GF, Benjamin EJ. Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. *Hypertension*. 2008;51:1651–1657.
 38. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. *J Hum Hypertens*. 2005;19:149–154.
 39. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension*. 2001;38:399–403.
 40. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005;352:48–62.
 41. McComsey GA, Moser C, Currier J, Ribaldo HJ, Paczuski P, Dube MP, Kelesidis T, Rothenberg J, Stein JH, Brown TT. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. *Clin Infect Dis*. 2016;62:853–862.
 42. McComsey GA, Kitch D, Sax PE, Tebas P, Tierney C, Jahed NC, Myers L, Melbourne K, Ha B, Daar ES. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis*. 2011;53:185–196.
 43. Joy T, Keogh HM, Hadigan C, Dolan SE, Fitch K, Liebau J, Johnsen S, Lo J, Grinspoon SK. Relation of body composition to body mass index in HIV-infected patients with metabolic abnormalities. *J Acquir Immune Defic Syndr*. 2008;47:174–184.
 44. Lichtenstein KA, Armon C, Buchacz K, Chmiel JS, Moorman AC, Wood KC, Holmberg SD, Brooks JT; HIV Outpatient Study Investigators. Initiation of antiretroviral therapy at CD4 cell counts ≥ 350 cells/mm³ does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency. *J Acquir Immune Defic Syndr*. 2008;47:27–35.

SUPPLEMENTAL MATERIAL

Table S1. Distribution (number and percent) of specific ART used for the first regimen and total follow-up time spent taking a specific ART (Person Years, percent of follow-up).

	Immediate		Deferred	
	First Regimen N(%) [*]	Cumulative Follow-up Time on Drug PY(% time) [†]	First Regimen N(%) [*]	Cumulative Follow-up Time on Drug PY(% time) [†]
No. of participants	2326		2359	
Any NRTI	2285 (98.2)	6582 (93.9)	1131 (47.9)	1954 (27.7)
Abacavir	72 (3.1)	344 (4.9)	70 (3.0)	154 (2.2)
Emtricitabine	2025 (87.1)	5794 (82.7)	1001 (42.4)	1724 (24.4)
Tenofovir	2026 (87.1)	5821 (83.1)	1012 (42.9)	1735 (24.6)
Lamivudine	260 (11.2)	779 (11.1)	129 (5.5)	225 (3.2)
Zidovudine	188 (8.1)	411 (5.9)	47 (2.0)	63 (0.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any NNRTI	1759 (75.6)	4524 (64.6)	722 (30.6)	1122 (15.9)
efavirenz	1661 (71.4)	4097 (58.5)	573 (24.3)	855 (12.1)
rilpivirine	97 (4.2)	360 (5.1)	141 (6.0)	237 (3.4)
other	1 (0.0)	68 (1.0)	8 (0.7)	31 (0.4)
Any PI	424 (18.2)	1653 (23.6)	252 (10.7)	553 (7.8)
atazanavir	230 (9.9)	887 (12.7)	99 (4.2)	220 (3.1)
darunavir	165 (7.1)	611 (8.7)	125 (5.3)	290 (4.1)
fosamprenavir	11 (0.5)	33 (0.5)	6 (0.3)	13 (0.2)
lopinavir	18 (0.8)	121 (1.7)	21 (0.9)	30 (0.4)
ritonavir	422 (18.1)	1630 (23.3)	250 (10.6)	547 (7.8)
other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any INSTI	103 (4.4)	448 (6.4)	157 (6.7)	288 (4.1)
dolutegravir	1 (0.0)	10 (0.1)	19 (0.8)	21 (0.3)
elvitegravir	1 (0.0)	25 (0.4)	49 (2.1)	63 (0.9)
raltegravir	101 (4.3)	413 (5.9)	89 (3.8)	205 (2.9)
other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other ART [‡]	1 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)

Not on any ART	39 (1.7)	400 (5.7)	1225 (51.9)	5094 (72.2)
----------------	----------	-----------	-------------	-------------

N – number; *PY* – Person years; *ART* – Antiretroviral therapy; *NRTI* – nucleoside reverse transcriptase inhibitor; *NNRTI* – non-nucleoside reverse transcriptase inhibitor; *PI* – protease inhibitor; *INSTI* – integrase strand transfer inhibitor

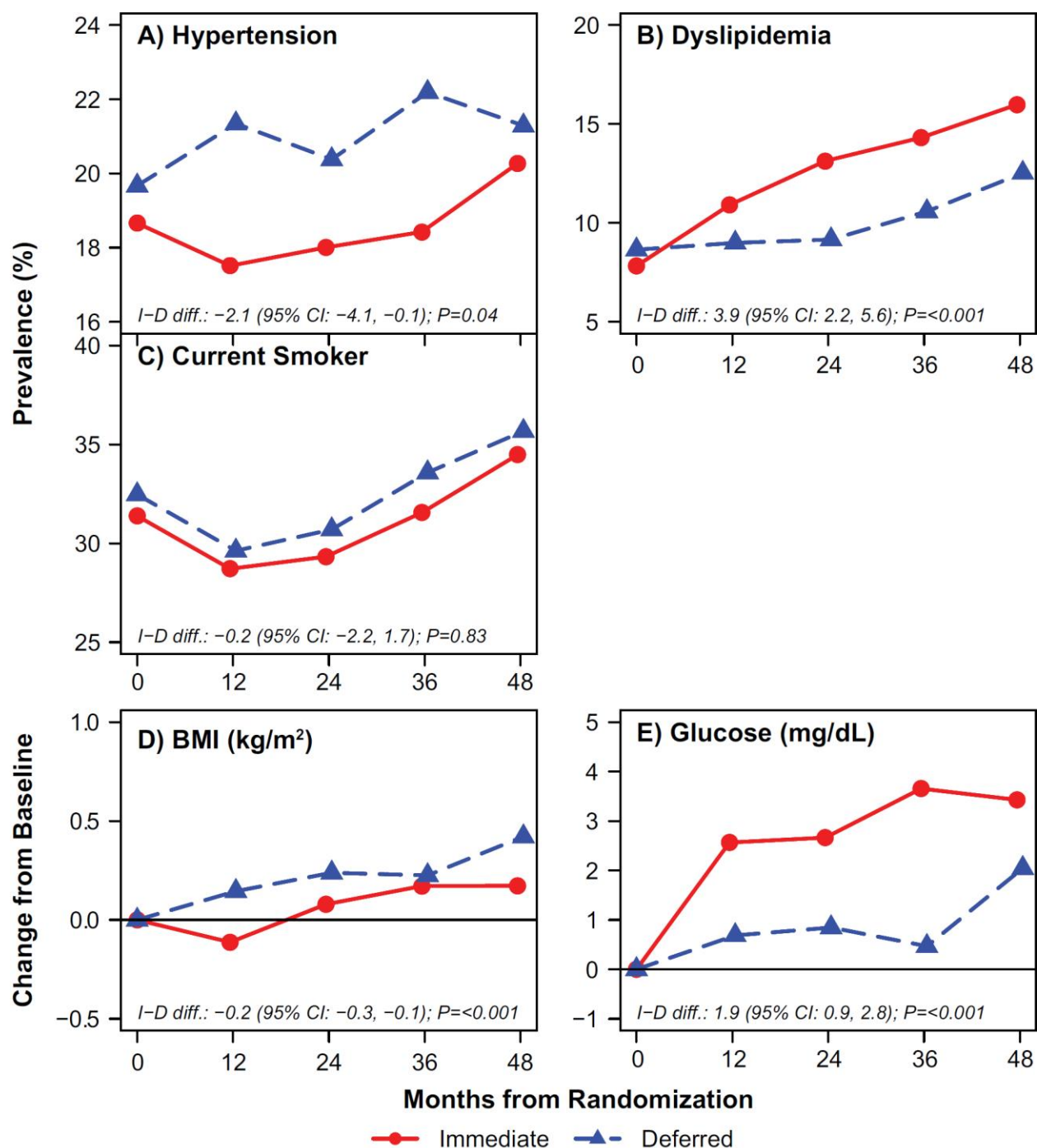
* Denominator is all participants in the randomization group.

† Person years includes switches and accounts for stops and therefore includes time spent on drug for participant who did not initiate ART with the given

drug. Denominator is over all follow-up time accumulated within the randomization group.

‡ 1 participant started a blinded study and the type of ART taken is unknown.

Figure S1. Changes in the Prevalence of Selected CVD Risk Factors by Treatment Group



Shown in panels A-C is the unadjusted prevalence (%) at baseline and follow-up annual visits for participants in the immediate (I, solid line) and deferred (D, dashed line) ART groups for CVD (cardiovascular disease) risk factor, including hypertension (panel A), dyslipidemia (panel

B), and current smoking (panel C). Presented within panels A-C are overall estimated differences in prevalence (with 95% confidence interval and p-value) over follow-up between the two groups (immediate minus deferred), adjusting for the baseline prevalence and visit from generalized estimating equations. Shown in panels D-E are the unadjusted mean changes from baseline at annual visits for participants in both ART groups for the following measures: body mass index (BMI, panel D) and glucose (panel E). Presented within panels D-E is the estimated mean difference (with 95% confidence interval and p-value) over follow-up between the two groups (immediate minus deferred), adjusting for the baseline value and visit from longitudinal mixed models. Figures are truncated at Month 48.

Appendix: The INSIGHT START (Strategic Timing of AntiRetroviral Treatment) Study Group

In addition to writing group, the following committee members contributed to the conduct of the START trial:

Community Advisory Board: C. Rappoport (INSIGHT community liaison), P.D. Aagaard, S. Collins, G.M. Corbelli, N. Geffen, C. Kittittrakul, T. Maynard, M. Meulbroek, D. Munroe, M.S. Nsubuga, D. Peavey, S. Schwarze, M. Valdez.

Substudy Chairs: J.V. Baker, D. Duprez (arterial elasticity); A. Carr, J. Hoy (bone mineral density); M. Dolan, A. Telenti (genomics); C. Grady (informed consent); G. Matthews, J. Rockstroh (liver fibrosis progression); W.H. Belloso, J.M. Kagan (monitoring); E. Wright, B. Brew, R.W. Price, K. Robertson, L. Cysique (neurology); K.M. Kunisaki, J.E. Connett, D.E. Niewoehner (pulmonary). Endpoint Review Committee: A. Lifson (chair), W.H. Belloso, R.T. Davey Jr., D. Duprez, J.M. Gatell, J. Hoy, C. Pedersen, R.W. Price, R. Prineas, J. Worley.

Central Drug Repository and Drug Distribution: K. Brekke, S. Meger, B. Baugh, J. Eckstrand, C. Gallagher, J. Myers, J. Rooney, J. Van Wyk.

Network Laboratory Group: J. Baxter, C. Carey, A. DuChene, E.B. Finley, M. George, J. Garup, M. Hoover, R. Pedersen, C. Russell, B. Standridge.

Specimen Repositories: E. Flowers, M. Hoover, K. Smith (Advanced BioMedical Laboratories, LLC, Cinnaminson, NJ, United States); M. McGrath, S. Silver (AIDS and Cancer Specimen Resource, University of California, San Francisco, San Francisco, CA, United States).

Wake Forest ECG Reading Center, Winston-Salem, NC, United States: E.Z. Soliman, M. Barr, C. Campbell, S. Hensley, J. Hu, L. Keasler, Y. Li, T. Taylor, Z.M. Zhang.

Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD, United States: B. AlstonSmith, E. DeCarlo, K. Klingman, M. Proschan.

Data and Safety Monitoring Board: S. Bangdiwala (chair), R. Chaisson, A.R. Fleischman, C. Hill, J. Hilton, O.H.M. Leite, V.I. Mathan, B. Pick, C. Seas, P. Suwangool, G. Thimothé, F. Venter, I. Weller, P. Yeni.

Minnesota Coordinating Center, University of Minnesota, Minneapolis, MN, United States: J.D. Neaton, K. Brekke, G. Collins, E.T. Denning, A. DuChene, N.W. Engen, M. George, B. Grund, M. Harrison, K.H. Hullsiek, L.H. Klemme, E. Krum, G. Larson, S. Meger, R. Nelson, J. Neuhaus Nordwall, K. Quan, S.F. Quan, T. Schultz, S. Sharma, G. Thompson.

International Coordinating Centers: *Copenhagen HIV Programme, Rigshospitalet, University of Copenhagen, Denmark:* J.D. Lundgren, B. Aagaard, A.H.D. Borges, M. Eid, J. Grarup, P. Jansson, Z. Joensen, B. Nielsen, M. Page 3 Pearson, R. Pedersen, A.N. Phillips; *The Kirby Institute, University of New South Wales, Sydney, Australia:* S. Emery, N. Berthon-Jones, C. Carey, L. Cassar, M. Clewett, D. Courtney-Rodgers, P. Findlay, S. Hough, S. Jacoby, J. Levitt, S.L. Pett, R. Robson, V. Shahamat, A. Shambrook; *Medical Research Council Clinical Trials Unit at UCL, London, United Kingdom:* A.G. Babiker, B. Angus, A. Arenas-Pinto, R. Bennett, N. Braimah, E. Dennis, N. Doyle, M. Gabriel, F. Hudson, B. Jackson, A. Palfreeman, N. Paton, C. Purvis, C. Russell; *Veterans Affairs Medical Center, Washington, DC, United States:* F. Gordin, D. Conwell, H. Elvis, E.B. Finley, V. Kan, L. Lynch, J. Royal, A. Sánchez, B. Standridge, D. Thomas, M. Turner, M.J. Vjecha.

The following investigators participated in the START study, listed by country (country lead, numbers of participants enrolled) and clinical site:

Argentina (M.H. Losso, n=216): CAICI (Instituto Centralizado de Asistencia e Investigación Clínica Integral), Rosario Santa Fe: S. Lupo, L. Marconi, D. Aguila; FUNCEI, Buenos Aires: G. Lopardo, E. Bissio, D. Fridman; Fundación IDEAA, Buenos Aires: H. Mingrone, E. Loiza, V. Mingrone; Hospital General de Agudos JM Ramos Mejía, Buenos Aires: M. Losso, J.M. Bruguera, P. Burgoa; Hospital Interzonal General de Agudos Dr. Diego Paroissien, Buenos Aires: E. Warley, S. Tavella; Hospital Italiano de Buenos Aires, Buenos Aires: W. Belloso, M. Sanchez; Hospital Nacional Profesor Alejandro Posadas, Buenos Aires: H. Laplumé, L. Daciuk; Hospital Rawson, Cordoba: D. David, A. Crinejo; Argentinean SCC, Fundación IBIS, Buenos Aires: G. Rodriguez-Loria, L. Doldan, A. Moricz, I. Otegui, I. Lanusse.

Australia (J. Hoy, n=109): Burwood Road General Practice, Burwood, VIC: N. Doong, S. Hewitt; Centre Clinic, St Kilda, VIC: B.K. Tee; East Sydney Doctors, Darlinghurst, NSW: D. Baker, E. Odgers; Holdsworth House Medical Practice, Darlinghurst, NSW: S. Agrawal, M. Bloch; Melbourne Sexual Health Centre, Carlton, VIC: T.R.H. Read, S.J. Kent; Prahran Market Clinic, Prahran, VIC: H. Lau, N. Roth; Royal Adelaide Hospital, Adelaide, SA: L. Daly, D. Shaw; Royal Perth Hospital, Perth, WA: M. French, J. Robinson; Sexual Health & HIV Service - Clinic 2, Brisbane, QLD: M. Kelly, D. Rowling; St Vincent's Hospital, Fitzroy, VIC: D.A. Cooper, A. J. Kelleher; Taylor Square Private Clinic, Surry Hills, NSW: C. Pell, S. Dinning; The Alfred Hospital, Melbourne, VIC: J. Hoy, J. Costa; Westmead Hospital, Westmead, NSW: D.E. Dwyer, P. King.

Austria (A. Rieger, n=7): Otto-Wagner-Spital SMZ /Baumgartner Hoehe, Vienna: N. Vetter; B. Schmied; University Vienna General Hospital, Vienna: A. Rieger, V.R. Touzeau.

Belgium (S. de Witt, n=102): Centre Hospitalier Universitaire St. Pierre (C.H.U. St. Pierre), Brussels: S. de Witt, N. Clumeck, K. Kabeya; Institute of Tropical Medicine, Antwerp: E. Cleve, E. Florence, L. van Petersen; Universitair Ziekenhuis Gasthuisberg, Leuven: H. Ceunen, E.H. van Wijngaerden; Universitaire Ziekenhuizen Gent, Gent: T. James, L. Vandekerckhove.

Brazil (L.C. Pereira Jr., M. Schechter, n=619): Ambulatório de Imunodeficiências (LIM-56), Sao Paulo, SP: J. Casseb, E. Constantinov, M.A. Monteiro; Center for ID at UFES, Vitoria, ES: L.N. Passos, T. Reuter; Centro de Referência e Treinamento DST/AIDS, Sao Paulo, SP: S.T. Leme, J.V.R. Madruga, R.S. Nogueira; Hospital Page 4 Escola Sao Francisco de Assis, Rio de Janeiro, RJ: M. Barbosa Souza, C. Beppu Yoshida, M. Dias Costa; Instituto de Infectologia Emilio Ribas, Sao Paulo, SP: R. Castro, R.Cruz, S. Ito, T.N. Lobato Souza; Instituto FIOCRUZ, Rio de Janeiro, RJ: B. Grinsztejn, V.G. Veloso, S. Wagner Cardoso; SEI Serviços Especializados em Infectologia LTDA, Salvador, Bahia: F. Bahia, C. Brites, J. Correia.

Chile (M.J. Wolff, n=76): Fundación Arriarán, Santiago: M. Wolff, R. Northland, C. Cortés.

Czech Republic (D. Sedlacek, n=13): Faculty Hospital Na Bulovce, Prague: D. Jilich; University Hospital Plzen, Plzen: D. Sedlacek.

Denmark (J. Gerstoft, n=33): Hvidovre University Hospital, Hvidovre: P. Collins, L. Mathiesen; Odense University Hospital, Odense: L. Hergens, C. Pedersen; Rigshospitalet, Copenhagen: J. Gerstoft, L.P. Jensen; Århus Universitetshospital, Skejby, Århus: I.R. Lofthiem, L. Østergaard.

Estonia (K. Zilmer, n=8): West Tallinn Central Hospital Infectious Diseases, Tallinn: K. Zilmer.

Finland (M. Ristola, n=23): Helsinki University Central Hospital, Helsinki: M. Ristola, O. Debnam.

France (B. Hoen, n=111): CHU Côte de Nacre – Caen, Caen: R. Verdon, S. Dargere; CHU de Besançon - Hôpital Jean-Minjoz, Besancon: B. Hoen, C. Chirouze; Groupe Hospitalier Pitié-Salpêtrière, Paris: C. Katlama, M-A. Valantin; Hôpital Antoine Bécélère, Clamart: F. Boue, I. Kansau; Hôpital de Bicêtre, Le Kremlin-Bicetre: C. Goujard, C. Chakvetadze; Hôpital Européen Georges Pompidou, Paris: L. Weiss, M Karmochkine; Hôpital Foch, Suresnes: D. Zucman, C. Majerholc; Hôpital Gustava Dron, Tourcoing: O.Robineau, R. Biekre; Hôpital Henri Mondor, Creteil: Y. Levy, J.D. Lelievre; Hôpital Hôtel Dieu, Paris: J.P. Viard, J Ghosn; Hôpital Saint-Antoine, Paris: J. Pacanowski, B. Lefebvre; Hôpital Saint-Louis, Paris:

J.-M. Molina, L. Niedbalski, M. Previlon; French SCC, ANRS-Inserm SC10, Paris: J.P. Aboulker, C. Capitant, B. Lebas, N. Leturque, L. Meyer, E. Netzer.

Germany (G. Fätkenheuer, n=312): EPIMED, Berlin: K. Arastéh, T. Meier; Gemeinschaftspraxis Jessen-JessenStein, Berlin: C. Zedlack, H. Jessen; ICH Study Center, Hamburg: S. Heesch, C. Hoffmann; Ifi - Studien und Projekte GmbH, Hamburg: A. Plettenberg, A. Stoehr; Johann Wolfgang Goethe - University Hospital, Frankfurt: G. Sarrach, C. Stephan; Klinik I für Innere Medizin der Universität zu Köln, Cologne: G. Fätkenheuer, E. Thomas; Klinikum der Universität München, Munich: J.R. Bogner, I. Ott; Klinikum Dortmund GmbH, Dortmund: M. Hower, C. Bachmann; Medizinische Hochschule Hannover, Hannover: M. Stoll, R. Bieder; Medizinische Universitätsklinik - Bonn, Bonn: J. Rockstroh, B. Becker; Universitätsklinikum Düsseldorf, Düsseldorf: B. Jensen, C. Feind; Universitätsklinikum Erlangen, Erlangen: E. Harrer, T. Harrer; Universitätsklinikum Essen, Essen: S. Esser, H. Wiehler; Universitätsklinikum Heidelberg, Heidelberg: M. Hartmann, R. Röger; Universitätsklinikum Regensburg, Regensburg: B. Salzberger, E. Jäger; Universitätsklinikum Würzburg, Würzburg: H. Klinker, G. Mark; Universitätsklinikum, Hamburg-Eppendorf: J. van Lunzen, N. Zerche; German SSC, Johann Wolfgang Goethe - University Hospital, Frankfurt: V. Müller, K. Tillman.

Greece (G. Touloumi, n=101): AHEPA University Hospital, Thessaloniki Central Macedonia: S. Metallidis, O. Tsachouridou; Attikon University General Hospital, Athens: A. Papadopoulos, K. Protopapas; Evangelismos General Hospital, Athens: A. Skoutelis, V. Papastamopoulos; Hippokration University General Hospital of Athens, Athens: H. Sambatakou, I. Mariolis; Korgialenio-Benakio Hellenic Red Cross, Athens: M. K. Lazanas, M. Chini; Syngros Hospital, Athens: S. Kourkounti, V. Paparizos; Greek SCC, National Kapodistrian University of Athens, Athens: G. Touloumi, V. Gioukari, O. Anagnostou.

India (n=91): Institute of Infectious Diseases, Pune Maharashtra: A. Chitalikar, S. Pujari; YRGCARE Medical Centre VHS, Chennai CRS: F. Beulah, N. Kumarasamy, S. Poongulali.

Ireland (P. Mallon, n=7): Mater Misericordiae University Hospital, Dublin: P. Mallon, P. McGettrick.

Israel (E. Kedem, n=28): Rambam Medical Center, Haifa: E. Kedem, S. Pollack; Tel Aviv Sourasky Medical Center, Tel Aviv: D. Turner.

Italy (G. Tambussi, n=33): Lazzaro Spallanzani IRCSS, Rome: A. Antinori, R. Libertone; Ospedale San Raffaele S.r.l., Milan: G. Tambussi, S. Nozza, M.R. Parisi.

Luxembourg (T. Staub, n=5): Centre Hospitalier de Luxembourg, Luxembourg: T. Staub, C. Lieunard.

Malaysia (n=18): University Malaya Medical Centre, Kuala Lumpur: R.I.S.R. Azwa.

Mali (S. Dao, n=41): SEREFO/ CESAC Mali, Bamako, Bamako: B. Baya, M. Cissé, D. Goita.

Mexico (n=48): INCMNSZ (Instituto Nacional de Ciencias Médicas y Nutrición), Tlalpan D.F.: J. Sierra-Madero, M.E. Zghaib.

Morocco (K.M. El Filali, n=44): University Hospital Centre Ibn Rochd, Casablanca: K.M. El Filali, I. Erradey, H. Himmich.

Nigeria (n=50): Institute of Human Virology-Nigeria (IHVN), Garki, Abuja FCT: E. Ekong, N. Eriobu.

Norway (V. Ormaasen, n=15): Oslo University Hospital, Ulleval, Oslo: V. Ormaasen, L. Skeie.

Peru (A. La Rosa, n=215): Hospital Nacional Edgardo Rebagliati Martins, Lima, Lima: M. Espichan Gambirazzio, F. Mendo Urbina; Hospital Nacional Guillermo Almenara Irigoyen, Lima, Lima: R. Salazar Castro, J. Vega Bazalar; IMPACTA Salud y Educación, Lima, Lima: M.E. Guevara, R. Infante, J. Sanchez, M. Sanchez; IMPACTA San Miguel, Lima, Lima: R. Chinchay, J.R. Lama, M. Sanchez; Via Libre, Lima, Lima: E.C. Agurto, R. Ayarza, J.A. Hidalgo.

Poland (A.J. Horban, n=68): EMC Instytut Medyczny SA, Wroclaw: B. Knysz, A. Szymczak; Uniwersytecki Szpital Kliniczny, Bialystok: R. Flisiak, A. Grzeszczuk; Wojewodzki Szpital Zakazny, Warsaw: A.J. Horban, E. Bakowska, A. Ignatowska.

Portugal (L. Caldeira, n=67): Hospital Curry Cabral, Lisbon: F. Maltez, S. Lino; Hospital de Egas Moniz, Lisbon: K. Mansinho, T. Baptista; Hospital de Santa Maria, Lisbon: M. Doroana, A. Sequeira, L. Caldeira; Hospital Joaquim Urbano, Oporto: J. Mendez, R.S.E. Castro.

South Africa (R. Wood, n=518): 1 Military Hospital, Pretoria Gauteng: S.A. Pitsi; Desmond Tutu HIV Centre - Cape Town, Cape Town, Western Province: R. Kaplan, N. Killa, C. Orrell, M. Rattley; Durban International Clinical Research Site, Durban, KwaZulu Natal: U.G. Lalloo, R. Mngqibisa, S. Pillay; Durban International Clinical Research Site WWH, Durban, KwaZulu Natal: J. Govender, M. John; University of Witwatersrand, Johannesburg, Gauteng: S. Badal-Faesen, N. Mwelase, M. Rassool.

Spain (J.R. Arribas, n=234): Complejo Hospitalario Xeral Cies, Vigo Pontevedra: A.O. Hermida, F. Warncke; Hospital Clínic de Barcelona, Barcelona: J.M. Gatell, A. Gonzalez; Hospital Clínico San Carlos, Madrid: V. Estrada, M. Rodrigo; Hospital de la Santa Creu i Sant Pau, Barcelona: P. Domingo, M. Gutierrez; Hospital del Mar, Barcelona: H.J. Knobel, A. Gonzalez; Hospital La Paz, Madrid: J.R. Arribas, M. Montes Ramirez; Hospital La Princesa, Internal Medicine and Infectious Disease Service CRS, Madrid: I. de los Santo Gil, J. Sanz Sanz; Hospital Universitari Germans Trias i Pujol, Badalona: B. Clotet, J.M. Llibre, P. Cobarsi; Hospital Universitari Mutua Terrassa, Terrassa Barcelona: D. Dalmau, C. Badia; Hospital Universitario Doce de Octubre, Madrid: R. Rubio, M.M. del Amo; Hospital Universitario Príncipe de Asturias, Alcala de Henares Madrid: J. Sanz Moreno; Hospital Universitario y Politécnico La Fe, Valencia: J. López Aldeguez, S. Cuellar; Spanish SSC, Acoiba, Madrid: P. López, B. Portas, P. Herrero.

Sweden (M. Gisslén, n=2): Sahlgrenska University Hospital, Sweden: M. Gisslén, L. Johansson; Skåne University Hospital, Malmö: C. Håkangård, K. Törqvist.

Switzerland (H. Furrer, n=31): Bern University Hospital, Bern: H. Furrer, A. Rauch; Unite VIH/SIDA Genève, Genève: A.L. Calmy, B. Hirschel (retd), T Lecompte; University Hospital Basel, Basel: M. Stoeckle; University Hospital Zurich, Zürich: N. Muller, M. Rizo-Oberholzer; Swiss SCC, Bern University Hospital, Bern: H. Furrer, C. Bruelisauer, A. Christen, M. Lacalamita.

Thailand (K. Ruxrungtham, n=248): Bamrasnaradura Infections Diseases Institute, Nonthaburi: W. Prasithsirikul, S. Thongyen; Chiangrai Prachanukroh Hospital, Chiang Rai: P. Kantipong, S. Khusuwan; Chonburi Regional Hospital, Chonburi: C. Bowonwatanuwong, U. Ampunpong; Chulalongkorn University Hospital, Bangkok: K. Ruxrungtham, A. Avihingsanon, W. Thiansanguankul; Khon Kaen University, Srinagarind Hospital, Khon Kaen: P. Chetchotisakd, P. Motsikapun, S. Anunnatsari; Ramathibodi Hospital, Bangkok: S. Kiertiburanakul, N. Sanmeema; Research Institute for Health Sciences (RIHES), Chiang Mai: K. Supparatpinyo, P. Sugandhavesa; Sanpatong Hospital, Chiang Mai: V. Klinbuayaem, Y. Siriwarothai; Siriraj Hospital, Bangkok Noi: W. Ratanasuwan, T. Anekthananon; Thai SCC, The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok: W. Harnnapachewin, T. Jupimai, P. Rerksirikul.

Uganda (P. Mugenyi, n=349): Joint Clinical Research Center (JCRC), Kampala: P. Mugenyi, C. Kityo, H. Mugerwa; MRC/UVRI Research Unit on AIDS, Entebbe: P. Munderi, B. Kikaire, J. Lutaakome; MRC/UVRI Research Unit on AIDS, Masaka – satellite site: Z. Anywaine.

United Kingdom (M.A. Johnson, n=339): Barts Health NHS Trust, London: C. Orkin, J. Hand; Belfast Health and Social Care Trust (RVH), Belfast Northern Ireland: C. Emerson, S. McKernan; Birmingham Heartlands Hospital, Birmingham West Midlands: D. White, C. Stretton; Brighton and Sussex University Hospitals NHS Trust, Brighton East Sussex: M. Fisher, A. Clarke, A. Bexley; Chelsea and Westminster Hospital, London: B. Gazzard, C. Higgs, A. Jackson; Coventry and Warwickshire NHS partnership Trust, Coventry West Midlands: S. Das, A. Sahota; Gloucestershire Royal Hospital, Gloucester: A. de Burgh-

Thomas, I. Karunaratne; Guy's and St. Thomas' NHS Foundation Trust, London: J. Fox, J.M. Tiraboschi; Imperial College Healthcare NHS Trust, London: A. Winston, B. Mora-Peris; Leicester Royal Infirmary, Leicester Leicestershire: M.J. Wiselka, L. Mashonganyika; Lewisham and Greenwich NHS Trust, London: S. Kegg, T. Moussaoui; North Manchester General Hospital, Manchester: E. Wilkins, Y. Clowes; Queen Elizabeth Hospital Birmingham, Birmingham West Midlands: J. Ross, J. Harding; Royal Berkshire Hospital, Reading Berkshire: F. Chen, S. Lynch; Royal Bournemouth Hospital, Bournemouth Dorset: E. Herieka, J. Ablorde; Royal Free London NHS Foundation Trust, London: M.A. Johnson, M. Tyrer, M. Youle; Sheffield Teaching Hospital NHS Foundation Trust, Sheffield South Yorkshire: D. Dockrell, C. Bowman; Southmead Hospital, Bristol: M. Gompels, L. Jennings; St. George's Healthcare NHS Trust, London: P. Hay, O. Okolo; The James Cook University Hospital, Middlesbrough Cleveland: D.R. Chadwick, P. Lambert; University College London Medical School, London: I. Williams, A. Ashraf.

United States (K. Henry, n=507): Adult Clinical Research Center, Newark, NJ: M. Paez-Quinde, S. Swaminathan; Boston University Medical Center, Boston, MA: I. Bica, M. Sullivan; Bronx-Lebanon Hospital Center, Bronx, NY: R.B. Cindrich, L.M. Vasco; Community Research Initiative of New England, Boston, MA: J. Green, H.B. Olivet; Cooper University Hospital, Camden, NJ: J. Baxter, Y. Smith; Cornell CRS, New York, NY: V. Hughes, T. Wilkin; Denver Public Health, Denver, CO: E.M. Gardner, J. Scott; Duke University, Durham, NC: J. Granholm, N. Thielman; Florida Department of Health in Orange/Sunshine Care Center, Orlando, FL: W.M. Carter, N.D. Desai; George Washington University Medical Center, Washington, DC: D.M. Parenti, G.L. Simon; Georgetown University Medical Center, Washington, DC: P. Kumar, M. Menna; Hennepin County Medical Center, Minneapolis, MN: J. Baker, R. Givot; Henry Ford Hospital, Detroit, MI: L.H. Makohon, N.P. Markowitz; Hillsborough County Health Department, Tampa, FL: M. Chow, C. Somboonwit; Infectious Disease Associates of Northwest Florida, Pensacola, FL: A.B. Brown, B.H. Wade; Lurie Children's Hospital, Chicago, IL: J. Jensen, A. Talsky; Maternal, Child and Adolescent Center for ID/Virology USC, Alhambra, CA: A. Kovacs, L. Spencer; Mayo Clinic, Rochester, MN: S. Rizza, Z. Temesgen; Medical College of Wisconsin, Milwaukee, WI: M. Frank, S. Parker; Montefiore Medical Center, Bronx, NY: C. Rosario, J. Shuter; Mt Sinai Hospital, Chicago, IL: K. Rohit, R. Yogev; National Military Medical Center, Bethesda, MD: I. Barahona, A. Ganesan; Naval Medical Center Portsmouth NMCP, Portsmouth, VA: S. Banks, T. Lalani; Naval Medical Center San Diego NMCS, San Diego, CA: M.F. Bavaro, S. Echols; NICE, Southfield, MI: M. Farrough, R.D. MacArthur; NIH, Bethesda, MD: R.T. Page 8 Davey Jr., R. McConnell; Ohio State University, Columbus, OH: H. Harber, S.L. Koletar; Orlando Immunology Center, Orlando, FL: E. DeJesus, A.F. Garcia; Regional Center for Infectious Disease, Greensboro, NC: K. Epperson, C.N. Van Dam; San Antonio Military Health System, JBSA Fort Sam Houston, TX: J.F. Okulicz, T.J. Sjoberg; San Juan Hospital, San Juan, PR: M. Acevedo, L. Angeli; St. Jude Children's Research Hospital, Memphis, TN: P.M. Flynn, N. Patel; Temple University, Philadelphia, PA: C. Geisler, E. Tedaldi; Texas Children's Hospital- Baylor College of Medicine, Houston, TX: C. McMullen-Jackson, W.T. Shearer; The Research & Education Group, Portland, OR: M.D. Murphy, S.M. Sweek; Tulane University Health Sciences Center, New Orleans, LA: D. Mushatt, C. Scott; UCLA CARE 4 Families, Los Angeles, CA: M. Carter, J. Deville; UCSD Mother-Child-Adolescent HIV Program, San Diego, CA: S.A. Spector, L. Stangl; University of Florida, Department of Pediatrics, Jacksonville, FL: M.H. Rathore, K. Thoma; University of Florida, Jacksonville, FL: M. Sands, N. Wilson; University of Illinois at Chicago, Chicago, IL: R.M. Novak, T. Pearson; University of Miami, Miami, FL: M.A. Kolber, T. Tanner; University of North Carolina, Chapel Hill, NC: M. Chicurel-Bayard, E. Hoffman; University of North Texas Health Science Center, Fort Worth, TX: I. Vecino, S.E. Weis; University of Puerto Rico, San Juan, PR: I. Boneta, J. Santana; University of Texas Southwestern Medical Center, Dallas, TX: M.K. Jain, M. Santos; Veterans

Affairs Greater LA Healthcare System, Los Angeles, CA: M.B. Goetz, W.L. Rossen; Virginia Commonwealth University, Richmond, VA: D. Nixon, V. Watson; Wake County Human Services, Raleigh, NC: D. Currin, C. Kronk; Wake Forest University Health Sciences, Winston-Salem, NC: L. Mosley, A. Wilkin; Washington DC Veterans Administration, Washington, DC: A.M. Labriola, D.W. Thomas; Yale University School of Medicine, New Haven, CT: D. Chodkowski, G. Friedland.

Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV–Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial

Jason V. Baker, Shweta Sharma, Amit C. Achhra, Jose Ignacio Bernardino, Johannes R. Bogner, Daniel Duprez, Sean Emery, Brian Gazzard, Jonathan Gordin, Greg Grandits, Andrew N. Phillips, Siegfried Schwarze, Elsayed Z. Soliman, Stephen A. Spector, Giuseppe Tambussi, Jens Lundgren and the INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group

J Am Heart Assoc. 2017;6:e004987; originally published May 22, 2017;
doi: 10.1161/JAHA.116.004987

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/6/5/e004987>